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REVIEW

Therapy of the refractory ascites: Total paracentesis vs. TIPS

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KEYWORDS
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Abstract This revision was aimed to report the evidences on the treatment of patients with cirrhosis and refractory ascites. Mainly, we wished to explore which of the predicting variables could be used to prefer large-volume paracentesis or TIPS.

PALABRAS CLAVE
Ascitis;
Cirrosis;
Paracentesis;
TIPS;
Metaanálisis

Tratamiento de la ascitis refractaria: paracentesis total frente a derivación portosistémica intrahepática transyugular

Resumen Esta revisión tiene el objetivo de describir las pruebas del tratamiento de pacientes con cirrosis y ascitis refractaria. Se ha quedo explorar en especial cuáles son las variables predictivas para preferir una paracentesis de gran volumen o derivación portosistémica intrahepática transyugular (TIPS).

During the natural history of cirrhosis an increased renal reabsorption of sodium and water which generates edema is a serious complication of portal hypertension. In fact, the first episode of ascites is a turning point of the disease which announces the risk of other complications of cirrhosis such as renal failure, hyponatremia, encephalopathy, variceal bleeding and bacterial infections.[1]

Causes of ascites and its complications

All these complications develop because of two pathophysiological events. First, the increase of portal pressure causes peritoneal accumulation of fluids (ascites) in consequence of a high filtration rate at the sinusoidal level. Second, the peripheral release of potent vasodilators, mainly in the splanchnic vascular bed, causes a hyperdynamic circulation with high cardiac output and low peripheral resistances.[2] The shift of a considerable blood volume from the central vascular bed to the splanchnic vessels determines a

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condition of ''effective hypovolemia'' which in turn stimulates the release of vasoconstrictors and further increases the renal sodium retention. The excess of vasoconstrictors can be detrimental for the kidney, the brain, and also for the cardiac fibers with an impaired cardiac contractility.[3]

Moreover, patients with cirrhosis and ascites are frequentely complicated by acute episode of bacterial infection.[4] The risk factors of infection in cirrhosis are represented by bacterial translocation and by a compromised function of the body defense mechanisms.[5]

Definition and prognosis of refractory ascites

In most patients with cirrhosis and ascites a low sodium diet combined with diuretic medications obtains the disappearance of ascites. However, in 10–15% of patients ascites is ''refractory'' and it cannot be resolved by this therapy. In these cases the administration of diuretic drugs is insufficient to increase urinary sodium excretion (diuretic-resistant ascites) or, more often, the diuretic therapy cannot be tolerated because of serious side-effects, such as encephalopathy, hyponatremia, renal failure (diuretic intractable ascites).[6,7]

Recently, the most accepted criteria for defining refractory ascites are an ascites that cannot be mobilized or whose re-accumulation after large-volume paracentesis (LVP) cannot be prevented by medical therapy.

Requirements for the diagnosis of refractory ascites are: (1) the patient should be on intensive diuretic therapy (spironolactone 400 mg/day + furosemide 160 mg/day) and on a salt poor diet (sodium <90 meq/day) by at least 1 week, (2) during treatment the body weight decreases by less than 200 g/day, (3) urine sodium excretion is less than sodium intake, (4) ascites gradually reappears within a short period of time after LVP.

By contrast, diuretic intractable ascites is characterized by the development of a diuretic-related complications such as hepatic encephalopathy in the absence of precipitating factors, an increase of serum creatinine by >100% to a value >2.5 mg/dl, a decrease of serum sodium by >10 mmol/L to a serum sodium of <125 mmol/L; a change of potassium <3 mmol/L or >6 mmol/L despite appropriate measures.

The median survival of patients suffering from refractory ascites is approximately 6 months. Hence, refractory ascites is per se an indication to liver transplantation but most of such patients do not meet all the criteria to be included in a list of liver transplant. The causes of exclusion are advanced age, relevant comorbidities such as coronaropathy, other cardiac or vascular diseases, cancer. In addition some patients, although affected by a severe liver disease do not rich the threshold to be admitted.

Prevention of refractory ascites

To prevent or delay the occurrence of refractory ascites is a very important clinical issue.

Although there are no studies specifically aimed to explore this possibility, it is reasonable that refractory ascites could be prevented by stopping the progression of liver damage, as can be achieved by removing the etiologic factors of liver disease or by reducing the portal pressure. However, any specific approach, such as the antiviral/antifibrotic drugs, the reduction of portal pressure by medical therapy and other promising treatments[8–12] still need to be specifically tested against this important endpoint before promoting their effects.

Therapies of refractory ascites

Several strategies to treat refractory ascites have been developed and tested with observational studies, randomized trials, and meta-analysis. LVP with albumin and transjugular intrahepatic portosystemic shunt (TIPS) are the most used strategies, and they will be specifically discussed.

One of the first treatments of refractory ascites was peritoneo-venous shunt or LeVeen shunt.[13] This device removes the peritoneal fluid by a pressure gradient between peritoneal cavity and central vein, filters the fluid, and infuses it through a thoracic tube into the right atrium. The rationale for using this device is to reduce the volume of ascites with a simultaneous re-expansion of the plasma volume. However, the success of the peritoneo-venous shunt was counterbalanced by the frequent occurrence of side-effects such as bacterial infections and occlusion of the filter. Moreover, two relevant RCTs demonstrated that the use of LeVeen shunt to treat tense ascites was not superior to the treatment with repeated LVP and albumin infusion.[14,15]

A more recent device to treat refractory ascites is Alpha Pump,[16] an implanted pump for the automated low-flow removal of ascites from the peritoneal cavity into the bladder. Alpha Pump, however, is an expensive device whose effects and safety still deserve to be ascertained by RCTs vs. LVP.

In the last years, a new family of orally active drugs, *vaptans*, that increase urine volume by the antagonism of the vasopressin V2 receptors have been tested for the treatment of the syndrome of inappropriate anti-diuretic hormone secretion (SIADH). These drugs, even if able to enhance solute free-water excretion and increase the serum sodium concentrations, did not demonstrate to be useful in the treatment of patients with refractory ascites.[17]

Large-volume paracentesis (LVP)

LVP, the direct aspiration of >5 L of ascites by a puncture of the abdominal wall, is widely used in clinical practice. Indeed, the rapid and complete efficacy in reducing ascites with rare complications made LVP (plus albumin) the first line of treatment for tense ascites. In addition, the efficacy and safety of treatment with LVP was validated by two RCTs vs. LeVeen shunt.[14,15]

The main complication of LVP is ''post-paracentesis circulatory-dysfunction'' (PPCD). It is a hemodynamic derangement with risk of detrimental clinical consequences. The diagnosis of PPCD requires a >50% increase of Plasma Renin Activity. This complication is often asymptomatic, but sometimes generates renal failure and hyponatremia. Mean survival is shorter in patients who develop PPCD compared to those who do not. To prevent PPCD an infusion of human albumin at the dose of 7–8 g per liter of fluid tapped is highly recommended. Accordingly, the rate of PPCD was approximately 70% after paracentesis without any re-expansion, 38% when combined with an infusion of dextran or gelatin

solutions and only 15% when taps are combined with albumin administration.

Other rare complications of LVP are intra-abdominal bleeding and bacterial infections. However, in a series of 515 procedures, De Gottardi et al.[18] reported a very low risk of complications involving only 1.6% of the procedures (intra-abdominal bleeding in five cases and bacterial infections in three). The same series showed that such complications were associated with a blood platelet count below 50,000/mm^3, a Child–Pugh class C, and an alcoholic etiology. Thus, caution should be adopted in patients who has reached these alterations.

TIPS (transgiugular-intrahepatic portosystemic shunt)

TIPS is a porto-systemic shunt obtained by an intravascular insertion of a stent bridging a portal branch with an hepatic vein. This procedure causes a fall of portal pressure with reduction of the vascular collateral circulation. A further important effect of TIPS is the increase of central blood volume with potential improvement of renal function. At today, the main indications for TIPS are: (a) the portal hypertension-related bleeding with high mortality risk, ''early TIPS'',[19] (b) failure of bleeding control by conservative methods ''rescue TIPS'',[20] and (c) refractory ascites.

In addition, in patients with advanced cirrhosis and ascites, TIPS can improve the nutritional status by favoring a nitrogen positive balance.[21] Perioperative-related risks of TIPS include intra-abdominal hemorrhage, accidental puncture of biliary or other vessels with development of *fistulae*, segmental hepatic ischemia, and stent infection (*endotipsitis*). All these complications are rare in expert hands. By contrast, the frequency is higher for long-term risks such as hepatic encephalopathy, the occlusion of the stent, hemolytic anemia, cardiac dysfunction.

Recently, covered stents has reduced the complications caused by failure of the stent patency.

This allows a stable hemodynamic result of the TIPS. Nevertheless, the risk of hepatic encephalopathy is still high and constitutes one of the most important limit to a larger use of TIPS. Accordingly, a strict selection of candidates could obviate most of such complications.

Refractory ascites: better TIPS or TAPS?

The disappearance of ascites observed in bleeding cirrhotic patients submitted to TIPS was the rationale for comparing LVP vs TIPS as a therapy of patients with refractory ascites. A meta-analyses conducted on four out of five RCTs showed that resolution of refractory ascites was significantly greater in patients treated with TIPS but the survival was only marginally better for TIPS patients.[22] However, a more in deep analysis using the individual data from the same four trials revealed that patients randomized to TIPS had a significant increase of the average survival of approximately 7 months.[23] Trials included into this analisis had used almost always bare stents, so it is possible that the survival advantage of TIPS will be larger using covered stents. Variables significantly associated with survival were age, serum bilirubin, and serum sodium. Accordingly, patients with refractory ascites showing normal values of these three variables were suggested to be the optimal candidates to be treated with TIPS.[23] By contrast, elevated serum bilirubin levels and reduced sodium levels, which were associated with an early death also by other studies on TIPS,[24,25] suggest to base the decision of treatment by taking into account also other clinical features, such as the pre-TIPS rate of LVP, nutritional status of the patient, the risk to develop disabling encephalopathy, and the patient ability to adhere to the pharmacological therapy. It is also recommendable to exclude TIPS in patients with a Child–Pugh score >11 or a MELD >18, particularly in patients who cannot become candidate to liver transplantation. The survival advantage observed in specific subgroups of patients treated with TIPS could be consequence of the low incidence of other complications due to portal hypertension. Indeed, Gines et al. demonstrated that patients receiving TIPS experience the lowest incidence of de novo hepatorenal syndrome (HRS) type 1 or progression from type 2 to type 1.[26] The meta-analysis by Salerno et al. demonstrated that patients treated with TIPS, compared to those treated with LVP, were less involved into the risk of spontaneous bacterial peritonitis, and gastrointestinal bleeding. Notwithstanding, all these advantages should be weighted with the consistent higher risk of encephalopathy.

Another important aspect to be taken into account is the impact of refractory ascites therapy on the quality of life. Moreover, a post hoc analysis from Campbell[27] demonstrated that patients with refractory ascites randomized to TIPS or LVP had similar alterations of their quality of life, due to the greater development of hepatic encephalopathy in patients receiving TIPS and to the more frequent taps in patients treated with LVP.

In conclusion it is important to remember that almost all the clinical observations of this paper come from studies in which bare-stents were used instead of covered-ones. Thus, the comparison between TIPS and LVP should be re-evaluated in the light of the stable hemodynamic effects achieved by the covered stents.

Conflict of interests

The authors declare no conflict of interest.

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